

Rare Case of Gamstorp-Wohlfart Syndrome in Northwestern India-A Case Report

Ira Chaudhary¹, Himanshu kaushal^{1*}, Rajendra Kumar Sureka², Aril Bhatia³

¹Senior Resident, Department of Neurology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India.

²Professor Emeritus, Department of Neurology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India.

³Senior Resident, Department of Neonatology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India.

*Corresponding author: Himanshu kaushal.

Abstract

We report a 15-year male with Gamstorp Wohlfart Syndrome from Rajasthan, India who presented with sensory motor neuropathy with asymmetric onset and neuromyotonia which was also confirmed on needle electromyography. His clinical exome analysis was carried out which showed that patient carried homozygous missense variant mutation in the coding exon 2 of HINT 1 gene p. Cys38Ter(c.114TC>A). Gamstorp wohlfart syndrome which is characterised by sensory motor (motor>sensory) or pure motor axonal neuropathy with distinctive feature of neuromyotonia which is usually associated with recessive HINT 1 mutation. The present case expands the geographic distribution of HINT 1 neuropathy in India. We confirm the association of hallmark sign of neuromyotonia with the disease.

Keywords: gamstorp wohlfart syndrome; HINT 1 gene; neuromyotonia; motor axonal neuropathy; charcot marrie tooth disease

Introduction

Peripheral nerve illnesses influenced by genetics are referred to as hereditary neuropathies (HN). When compared to other types of neuropathies, HN exhibit traits that distinguish their clinical, electrophysiological, and histological features [1]. One kind of HN that exhibits sensory deficiencies, musculoskeletal abnormalities such as pes cavus, claw toes, scoliosis, and central nervous system signs is called Charcot Marrie Tooth (CMT) illness. Although there are many cases of CMT presenting with sin-quan characteristics of different subtypes, myotonia and hereditary neuropathy are seldom associated and might provide a diagnostic challenge. The gene responsible for this uncommon combination is the histidine triad nucleotide-binding protein 1 (HINT1) gene. We report the case of a young guy with a mutation in the HINT1 gene here.

Case report

A 15 years old male child presented to our neurology OPD with complaints of change in gait for 4 years,

slippage of slippers from both feet, difficulty in walking for long distance and running since last 3 years. He also had difficulty in releasing hand after gripping something since last 2 months. His neurological examination revealed normal higher mental function and cranial nerve functions. There was no history of fasciculations. He had muscle atrophy of both thenar and hypothenar muscles (Figure 1.) with pes cavus of both feet. Tone was decreased in all four limbs. On manual muscle testing using medical research council scale power was 5/5 at both shoulder and elbow joint, 3/5 in flexors and 4/5 in extensors at wrist joint and hand grip was weak bilaterally. In the lower limb 5/5 at both hip joint, 4/5 at knee joint in both flexors and extensor, 3/5 in dorsiflexors on right side, 4/5 in dorsiflexors on left side and 4/5 in plantar flexors at the ankle joint bilaterally. There was presence of hand grip myotonia bilaterally without percussion myotonia. All deep tendon reflexes were absent and plantars were bilaterally flexors. There was no sensory loss. He had high steppage gait. The family history was also negative (Figure 2).



Figure 1: Thenar and Hypothenar Atrophy in Hands (Bilateral)

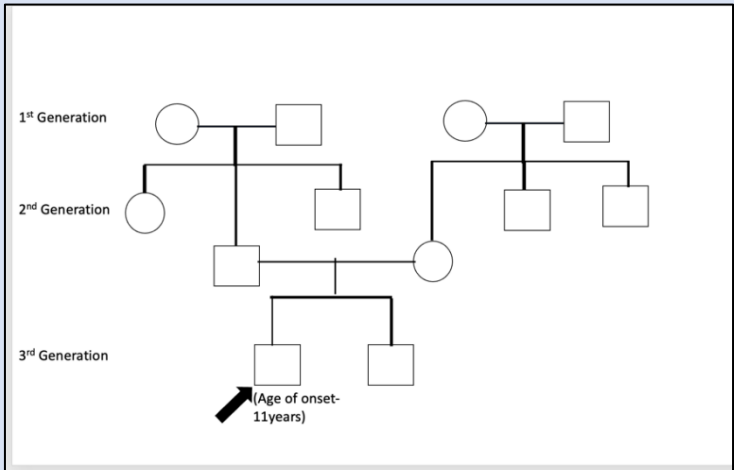


Figure 2: Pedigree chart of the patient’s family.

Diagnostic assessment

In laboratory workup elevated creatinine kinase was noted which was found to be 1051 U/L. Complete blood count and comprehensive metabolic panel was found to be normal. Nerve conduction studies (Table 1.) of both upper and lower limb demonstrated sensory-motor axonal affection in bilateral peroneal, tibial motor and bilateral sural sensory nerves. Motor-demyelinating affection was seen in right median nerve. Muscle biopsy from left biceps brachii (Figure 3) showed preserved fascicular architecture. The myofibers were polygonal and showed moderate variation in fiber size with few hypertrophic fibers showing splitting, with scattered atrophic angulated

fibers. There was no inflammation or ring fibers or fibers with internalised nuclei. These findings were suggestive of neurogenic changes. The patient was further subjected to a comprehensive clinical exome panel (Table 2.) which was suggestive of homozygous missense variant mutation in the coding exon 2 of HINT1 gene p.Cys38Ter(c.114TC>A) which was pathogenic and LRSAM1(+) While the in-silico prediction was inconclusive, the specific encoded amino acid (cysteine) was reported to be well-conserved in vertebrate species, and this variant may not be found in the healthy population. Our patient received phenytoin for myotonia and supportive care including orders for physical therapy and ankle foot orthosis.

Table 1: Nerve Conduction Study of both upper and lower limbs.

MOTOR NERVE STUDIES				
Nerve	Latency (ms)	Duration(ms)	Amplitude(mV)	NCV(m/s)
Right median				
Wrist	6.77	15	3.2	45.29
Elbow	12.29	12.29	3.0	NR
Axilla	NR	NR	NR	NR
Erbs	NR	NR	NR	NR
Left Median				
Wrist	6.8		2.1	46

	15			
Elbow	13.11	13.85	2.7	NR
Axilla	NR	NR	NR	NR
Wrist	NR	NR	NR	NR
Right Ulnar				
Wrist	4.90	10.31	3.9	52.94
Elbow	10.00	11.88	2.9	NR
Axilla	NR	NR	NR	NR
Erbs	NR	NR	NR	NR
Left Ulnar				
Wrist	4.91	11	3.6	51
Elbow	10.11	10.31	2.6	NR
Axilla	NR	NR	NR	NR
Erbs	NR	NR	NR	NR
Right Peroneal				
Ankle	NR	NR	NR	NR
Knee	NR	NR	NR	NR
Left Peroneal				
Ankle	NR	NR	NR	NR
Knee	NR	NR	NR	NR
Right Tibial				
Ankle	5.42	13.44	187.8	29.19
Knee	18.44	13.75	181.9	
Left tibial				
Ankle	4.69	11.04	0.6	31.72
Knee	16.67	13.85	0.4	NR
SENSORY NERVE STUDIES				
Upper limb				
Right Median				
Wrist	3.42	0.96	23.7	38.01
Left Median				
Wrist	2.9	0.92	25.1	42.1
Right Ulnar				
Wrist	2.92	0.96	14.5	44.52
Left Ulnar				
Wrist	2.90	0.98	17.1	45.1
Lower Limb				
Right Sural				
Mid-calf	NR	NR	NR	NR
Left Sural				
Mid-calf	NR	NR	NR	NR
Upper limb				
	M lat	Fmin Lat	Fmax Lat	Fmean Lat
Right Median	7.1	34.8	35.0	34.9
Left Median	2.7	29.2	29.2	29.2
Right Ulnar	4.2	31.9	31.9	31.9
Left Ulnar	1.9	30.4	30.4	30.4
Lower Limb				
Right Peroneal				
Right Peroneal	NR	NR	NR	NR
Left Peroneal				
Left Peroneal	NR	NR	NR	NR
Right Tibial				
Right Tibial	NR	NR	NR	NR
Left Tibial				
Left Tibial	NR	NR	NR	NR

(Abbreviations: F min Lat- F-wave minimum latency, F max Lat- F-wave maximum latency, F mean Lat- F- wave mean latency, ms- millisecond, mv- millivolt, m/s- meter/second, NR -Non-Recordable, M Lat- M-wave Latency)

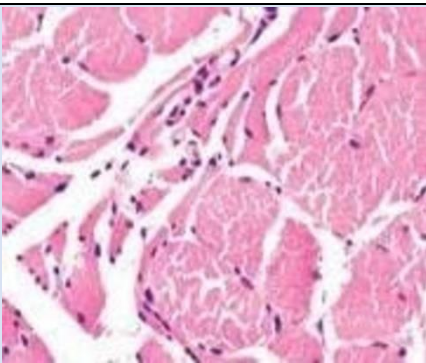


Figure 3: Muscle Biopsy from left biceps brachii showing histopathological changes of chronic neurogenic atrophy. Angulated atrophied muscle fibres arranged in groups are denervated motor units. The large size of the groups is suggestive of chronic neuropathic process.

Table 2: Clinical Exome Sequencing Report of the Patient.

Gene	Location	Variant	Zygosity	Disease	Inheritance	Classification
HINT1	Exon 2	C.114C>A(p.Cys38Ter)	Homozygous	Neuromyotonia and axonal neuropathy	Autosomal recessive	Pathogenic
LRSAM1(+)	Exon 17	C.1225C>A(p.Arg409Ter)	Homozygous	Charcot Marie Tooth disease Axonal type-2P	Autosomal dominant Autosomal recessive	Uncertain Significance

Discussion

With 79 people of Chinese, American, and European descent reported to date, HINT1 is a worldwide cause of CMT. Neuropathy with HINT1 has a non-random distribution. The bulk of those with diagnoses are from Europe [2]. To the best of our knowledge, we present Rajasthan, India's first instance of HINT1 neuropathy. The genotypic range of HINT1 mutations has been widened by our research. We have demonstrated that our patient carries the same new p.C38R mutation, which may be the product of a founder mutation in the Chinese population. Recessive HINT1 mutations are typically linked to sensory motor (motor>sensory) or pure motor axonal neuropathy with the characteristic trait of neuromyotonia [2]. HINT1 mutations account for around 2% of all CMT instances in genetically diverse patient cohorts, and for about 10%–12% of recessive CMT cases. However, this frequency increases to approximately 80% when axonal CMT patients with the characteristic neuromyotonia sign are taken into consideration [2-4].

High-frequency (150–220 Hz) repeated firing of a single motor unit is characteristic of neuromyotonia. Clinically, it appears as involuntary or provoked muscular contraction cramps, twitching of the muscles at rest, and poor relaxation of the muscles. It is thought to be a diagnostic feature of HINT1 and has been observed in 70–80% of patients. Since neuromyotonia is an extremely uncommon disorder, diagnosing it is not always simple [1]. By separating

Neuromyotonia with Axonal Neuropathy (NMN) from myotonic dystrophy and channelopathies that cause non-dystrophic myotonia, needle electromyography aids in the identification of neuromyotonia and narrows the differential diagnosis [2,5,6].

Our patient's clinical presentation matched previous reports of HINT1 neuropathy [5,7,8]. Our patient's onset occurred in first decade of life. By the time he came for consultation, he exhibited hand grip myotonia with pes cavus and asymmetric distal more than proximal weakness of all four limbs (lower limb>upper limb). Neuromyotonia was suggested by the usual repeated discharges of variable amplitude and frequency in a decremental pattern seen in needle EMG, whereas motor > sensory axonal neuropathy was revealed by nerve conduction investigations. Muscle biopsy from left biceps brachii showed neurogenic pattern. Based on the clinical presentation and molecular genetic analyses, a HINT1-related dHMN/motor-predominant polyneuropathy due to a novel p. Cys38Ter(c.114TC>A) mutation (homozygous missense) in the coding exon 2 of HINT1 was diagnosed in this patient. Treatment available for HINT1 neuropathies are only symptomatic and no definite therapy is available. The patients may benefit from physical therapy, ankle-foot orthoses and orthopedic corrections to maintain ambulation [2]. Myotonia which are disabling can be treated with sodium- channel blockers. In our case myotonia was present and was disabling for the patient and hence

was treated with phenytoin. He was on follow-up and showed improvement in his myotonia.

Conclusion

Hereditary neuropathies are rare entities. There is a wide array of manifestations in hereditary neuropathies. In a patient with young-onset neuropathy with features of hereditary neuropathy with neuromyotonia, one should keep the possibility of HINT1 gene mutation which can be easily missed on routine investigations.

References

1. Pisciotta C, Shy ME. (2023). Hereditary neuropathy. In: Motor System Disorders, Part I: Normal Physiology and Function and Neuromuscular Disorders. *Elsevier*, 609-617.
2. Peeters, K., Chamova, T., Tournev, I., & Jordanova, A. (2017). Axonal neuropathy with neuromyotonia: there is a HINT. *Brain*, 140:868-877.
3. Dohrn, M. F., Glöckle, N., Mulahasanovic, L., Heller, C., Mohr, J., Bauer, C., Riesch, E., Becker, A., Battke, F., Hörtnagel, K., Hornemann, T., Suriyanarayanan, S., Blankenburg, M., Schulz, J. B., Claeys, K. G., Gess, B., Katona, I., Ferbert, A., Vittore, D., Biskup, S. (2017). Frequent genes in rare diseases: panel-based next generation sequencing to disclose causal mutations in hereditary neuropathies. *Journal of Neurochemistry*, 143:507-522.
4. Zimon M, Baets J, Almeida-Souza L, De Vriendt E, Nikodinovic J, Parman Y, Battaloglu E, Matur Z, Guergueltcheva, V, Tournev, I, Auer-Grumbach M, De Rijk P, Petersen B-S, Müller T, Fransen E, Van Damme P, Löschner W N, Barišić N, Mitrovic Z, Jordanova A. (2012). Loss-of-function mutations in HINT1 cause axonal neuropathy with neuromyotonia. *Nature Genetics*, 44:1080-1083.
5. Jerath N U, Shy M E, Grider T, & Gutmann, L. (2015). A case of neuromyotonia and axonal motor neuropathy: A report of a HINT1 mutation in the United States. *Muscle and Nerve*, 52:1110-1113.
6. Wang Z, Lin J, Qiao K, Cai S, Zhang V, Zhao C, & Lu J. (2019). Novel mutations in HINT1 gene cause the autosomal recessive axonal neuropathy with neuromyotonia. *European Journal of Medical Genetics*, 62:190-194.
7. Rauchenzauner M, Frühwirth M, Hecht M, Kofler M, Witsch-Baumgartner M, & Fauth C. (2016). A novel variant in the HINT1 gene in a girl with autosomal recessive axonal neuropathy with neuromyotonia: Thorough neurological examination gives the clue. *Neuropediatrics*, 47:119-122.
8. Veltsista D, & Chroni E. (2016). A first case report of HINT1-related axonal neuropathy with neuromyotonia in a Greek family. *Clinical Neurology and Neurosurgery*, 148:85-87.

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